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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/055,817

01/23/2002

Philip Christopher Buxton

P32875-1

5917

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08/09/2004

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	<p>Application No.</p> <p>10/055,817</p>	<p>Applicant(s)</p> <p>BUXTON ET AL.</p>	
	<p>Examiner</p> <p>Gollamudi S Kishore, Ph.D</p>	<p>Art Unit</p> <p>1615</p>	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3-22-04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The request for the extension of time and amendment filed on 3-12-04 are acknowledged.

Claims included in the prosecution are 1-51.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 37-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites 'ratio of the filler to drug **in the granules**'; this implies that the granules are made from drug and the filler; it is

Inconsistent with claim 1, which appears to indicate that the salt of the compound is in the granular form. Similar is the case with claim 40, which recites 'granulation aid is present inside the granules of the composition'. Claims 47 and 48 recite 'intragranular ingredients' and claims 49-50 refer to granules prepared by wet granulation process. This terminology is confusing. What is in the granular form, the compound or the composition?

What is being conveyed by 'microcrystalline cellulose is present inside the granules of the composition is intragranular' recited in claim 51.

Claim Rejections - 35 USC # 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/18036 to Gaster et al., in view of Remington's Pharmaceutical Sciences and the International Cosmetic Ingredient Dictionary and Handbook. Gaster teaches Applicant's claimed compound and pharmaceutically acceptable salts thereof (claims 1-10). Gaster also teaches pharmaceutical compositions comprising the compound or salt thereof and pharmaceutically acceptable carriers. The compositions are usually adapted for oral, nasal, rectal, or parenteral administration, and may be in the form of tablets, capsules, oral liquid formulations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusible solutions or suspensions (page 7, lines 27- 38). Gaster teaches that the tablets and capsules are presented in a unit dosage form and contain conventional excipients, such as binders, fillers, diluents, tableting agents, lubricant, disintegrants, colorants, and others (page 8, lines 1-6). Gaster also teaches that the methods of making the compositions are traditional and known in the art (page 8, line 36). Gaster does not specifically teach the particle size of the invention. However, Gaster teaches that the formulation can be in powder, granular, tablet, or capsule form, and that the formulations can be made by methods traditionally known in the pharmaceutical art. Furthermore, absent a clear showing to the contrary, the

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determination of a particular particle size is well within the skill of the ordinary worker as part of the process of normal optimization,

particularly when the reference broadly teaches the use of granules, and trusts the skilled practitioner to follow conventional methods in making the described product.

Remington's Pharmaceutical Sciences, the 18th edition, is relied upon for the teaching that wet granulation is the most widely used and most general method of tablet preparation. The reference teaches that this popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. The reference also details the steps generally understood to be included in wet granulation. Furthermore, Gaster does not teach each of the specific excipients claimed by Applicant. However, The International Cosmetic Ingredient Dictionary and Handbook is relied upon to show that Applicant's choices for excipients are obvious selections. The reference teaches the use of calcium phosphate as a bulking agent, and hydroxypropyl methylcellulose and other celluloses as binders. The selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to Applicant's specific selection. For the above reasons, it is the position of the examiner that one skilled in the art would have been motivated to make a pharmaceutical composition comprising the active agent or a salt thereof disclosed by Gaster, in combination with a pharmaceutical carrier, based on the teachings of the reference. Furthermore, one would have been motivated to make the formulation using wet granulation, as that it taught as the most popular method of making tablets, and Gaster teaches to use conventional methods in making his

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formulations. The expected result would be a successful pharmaceutical formulation comprising the active agent taught by Gaster. Therefore, this invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. The newly added claim 35 recites crystallization of the compound and Gaster discloses the crystallization. The criticality of the amount of the compound and the ratios of the compound to the filler or granulation aid or disintegrant in the added claims is not readily apparent to the examiner since the amount of the active agent depends upon various parameters including the tolerability dose, the nature and severity of the disease. The amounts of the components in tablet formulations are deemed to be manipulatable parameters. The criticality of microcrystalline cellulose as the granulating aid or its amounts is also not readily apparent. As pointed out above, celluloses are known binders in formulations. Its routine use in tablets is also evident from the Handbook of Pharmaceutical excipients (page 102), which is already of record.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant while admitting that Gaster on page 7, lines 27-37 does disclose compositions containing a compound of the formula (I) or salt thereof which encompasses the claimed hydrochloride, argue that what Gaster teaches are Japanese-style granules wherein (usually) a spherical bead is coated with excipients and the drug, and the coated granules-rather than tablets- are administered orally directly to the patient and that passage does not disclose that the present hydrochloride particles themselves in granulated form. The examiner disagrees. Applicant's arguments that they are Japanese-style granules and are coated appear to be

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speculative since Gaster on line 31 states that the compositions are prepared by 'admixture' just as in instant invention as evident from claims 26 and 27 where the granules are prepared after mixing with fillers. Even assuming that Gaster teaches coated granules, it would be obvious to one of ordinary skill in the art, the compound itself is in the form of granules before they are coated since one cannot obtain a coated granule without the compound inside being granular. Furthermore, the criticality of this limitation is unclear to the examiner.

Applicant's arguments with regard to the teachings of Remington Pharmaceutical Sciences are not found to be persuasive. According to applicant, this reference indicates the acceptance of direct compression as the preferred method for the future. This argument is not found to be persuasive since Remington Pharmaceutical Sciences shows the availability of several methods of preparation and it is within the skill of the art to choose a method, which is well suited for his or her goals.

References CH-CZ3 are not considered since no documents have been found in the file.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

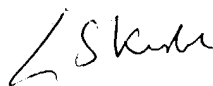
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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Gollamudi S Kishore, Ph.D
Primary Examiner
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GSK